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## **The serum bank of EuroPrevall - the prevalence, cost and basis of food allergy across Europe**

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van Ree, R ; Mills, C

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# The serum bank of EuroPrevall – The prevalence, cost and basis of food allergy across Europe

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## Abstract

EuroPrevall is an EU-funded multidisciplinary project including 62 institutions from 22 countries. EuroPrevall studies the prevalence and distribution of food allergies in infants, children, adolescents, and adults in Europe, threshold doses for allergenic foods, the role of the environment in food allergy, the socioeconomic impact of food allergy, and novel diagnostic tools for food allergies. The EuroPrevall serum bank (EPASB), containing samples from ~70,000 subjects, is a major tool to achieve these goals. EPASB is coordinated by the Paul-Ehrlich-Institut, Langen, Germany. Local sera collections are administered at the University of Amsterdam (NL), the University Hospital of Manchester (UK), Charité Hospital (DE) and the Paul-Ehrlich-Institut. The

EPASB coordinator and managing partners distribute samples for experimental work and regulate access. The overall aim is to provide sera to fulfil EuroPrevall research goals. The EPASB coordinator and managing partners suggest appropriate sera for addressing specific scientific and diagnostic questions. The serum bank will be maintained after termination of the project, but subsequent investigations must be in accordance with the original research goals of EuroPrevall. Thus, the contributors of the sera retain control over their future use. This rule prevents investigation of questions outside the scope of EuroPrevall, e.g. the allergenicity of genetically-modified foods.

**Keywords:** Allergenicity; Genetically-modified food; IgE; Atopic dermatitis; Pollen; Dust mite

**Abbreviations:** CRF, case record form; DBPCFC, double-blind placebo-controlled food challenge; EPASB, EuroPrevall serum bank; IP, integrated project; SME, small or medium-sized enterprise

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## 1. Introduction: The EuroPrevall project

EuroPrevall is an EU-funded multidisciplinary integrated project (IP) involving 16 European member states (Austria, Belgium, Czech Republic, Denmark, France, Germany, Greece, Hungary, Italy, Ireland, Lithuania, The Netherlands, Poland, Spain, Sweden, United Kingdom), Bulgaria (a candidate country), Switzerland, Iceland, Ghana, India, Russia, and China. An IP is a funding instrument to support objective-driven research, where the primary deliverable is new knowledge. IPs aim at either increasing Europe's competitiveness and addressing major needs in society. Their main tasks are to deliver knowledge for new products, processes, and services. In addition to a research component an IP may focus on technological development,

contain demonstration components, and contain a training component. EuroPrevall started in June 2005 (<http://www.euoprevall.org>) and will run for four years. Among the 62 partners (=participating research institute; clinic; small or medium-sized enterprise, SME), there are 18 clinical organisations, six SMEs as well as most of the leading allergy research organisations in Europe.

EuroPrevall aims at investigating the prevalence and distribution of food allergies throughout Europe in infants (birth cohorts in eight centres), children, adolescents, and adults (cross-sectional surveys in nine centres) (infant, 0–12 months, child, 1–12 years, adolescent, 13–18 years, adult 18 year and older). These wider-population studies will be complemented by more detailed studies based on referrals to allergy clinics at 12 centres. Detailed clinical data of all study subjects are entered directly to a web-accessible clinical databank by all clinical partners.

In more detail, the project aims at determining the threshold doses for different allergenic foods, investigating the role of the environment in determining the different patterns of food allergy, measuring the socioeconomic impact of food allergy, and at developing new diagnostic tools providing a better correlation of *in vitro* diagnostic results with the clinical situation. One important aspect in this context is the creation of a library of purified and well characterized natural and recombinant food allergens which will be used in a variety of diagnostic tests.

Moreover, the samples and information from the surveys will be used to identify risk factors (e.g. environmental, microbial or genetic) and novel predictive markers (e.g. biochemical and genetic) for food allergy, which might allow implementation of preventive measures (e.g. during pregnancy). Serological methods based on purified food allergens (“component-resolved diagnosis”) ([\[Bohle and Vieths, 2004\]](#) and [\[Lidholm et al., 2006\]](#)), including conventional and novel formats such as protein biochips ([\[Bacarese-Hamilton et al., 2005\]](#), [\[Dufva and Christensen, 2005\]](#), [\[Harwanegg and Hiller, 2004\]](#) and [\[Harwanegg and Hiller, 2005\]](#)) are developed to improve the quality of food allergy diagnosis and for reducing the need for food challenge tests.

In addition, partners investigate how food processing procedures and the food matrix affects allergenicity of foods, and develop new reference materials for food challenges that are based on real foods (e.g. confectionary). In the EuroPrevall

project these materials are professionally blinded meaning that the materials are evaluated by sensory panels (groups of testers who use their sensory faculties to describe food products on the basis of taste and smell). Procedures, tests, and questionnaires have been created and applied that can determine the impact of food allergies on the quality of life and its economic cost for food allergic people and their families, workplace and employers, and healthcare.

## **2. Aim of serological investigations within EuroPrevall**

It is planned to evaluate approximately 70,000 subjects within the different sub-studies of EuroPrevall: approximately 12,000 in the birth cohorts, 54,000 in the cross-sectional survey, approximately 1200 in the more detailed cross-sectional out patient studies, and 3000 from Ghana. Standard serology in EuroPrevall is performed with the ImmunoCAP system (Phadia, Uppsala, SE). In the wider-population studies, a standard battery of inhalants as well as commercially available and newly designed food mixes will be used for screening purposes. In the more detailed studies, sera from patients are tested for specific IgE against 12 respiratory allergen extracts (pollen of grasses, birch, live oak, cypress tree, plane tree, mugwort, Parietaria, white goosefood, ragweed; house dust mite, cat epithelium, dog epithelium), latex, and 24 different foods (hen's egg, cow's milk, peanut, soybean, hazelnut, walnut, celery, kiwi fruit, apple, peach, sesame seed, mustard seed, wheat, cod fish, shrimp, buck-wheat, corn, carrot, tomato, melon, banana, lentil, sunflower seed, poppy seed). These investigations provide basic information about sensitisation profiles in the different study populations and, by comparing the serological data with case histories or, in well defined subpopulations, with the results of double-blind placebo-controlled challenge tests, reveal information on the diagnostic performance of established *in vitro* tests, in particular on clinically false positive tests. Afterwards, studies will be designed with the aim to improve *in vitro* diagnosis utilising panels of purified allergen molecules derived from the EuroPrevall Allergen Library, established and novel IgE binding tests, and cellular *in vitro* assays (see below).

## **3. Clinical Databank**

The Clinical Databank is one of the central tools of the EuroPrevall project. It has been developed by Baigent Ltd., an SME company who is a full partner of

EuroPrevall. Data can be entered to the databank by clinical partners or laboratory scientists either directly online, or using offline versions of various case record forms (CRFs) and questionnaires developed by the clinical partners of EuroPrevall. The main aim of the clinical databank is to collect information from all clinical partners as well as laboratory data from various institutions in a uniform format. This approach will allow subsequent statistical evaluation of epidemiological and clinical data and selection of sera panels for further diagnostic studies and research studies on the structure, stability and biological activity of food allergens.

The quality of the clinical information obviously depends on the quality of the CRFs, which represent a key feature of the databank. For instance, six different CRFs have to be completed for each patient recruited within the cross-sectional study ( $n = 1200$  patients):

The “Background CRF” contains general data on the subjects, as well as case histories on allergy in general, including respiratory allergy, latex allergy, food allergy, atopic dermatitis, previous treatment by specific allergen immunotherapy.

One copy of the second “Food-CRF” is completed for each food to which the patients appear to be allergic. This CRF contains a very detailed evaluation of the case history including the kind of symptoms, symptom severity, time course of the reaction, amount of food causing a reaction, previous emergency treatment, and other information.

The third CRF summarises blood sampling data and results of skin prick tests which are performed with 42 different commercial extracts on each subject. Optional tickboxes are used for skin prick test results performed with fresh foods.

In the fourth CRF information on whether the patient meets the inclusion and exclusion criteria of the clinical study is recorded.

The fifth CRF collects detailed data on the results of double-blind placebo-controlled food challenges (DBPCFC).

In the sixth CRF, data on the results of open food challenges are recorded.

#### **4. Organisation and use of the EuroPrevall serum bank**

The EuroPrevall serum bank (EPASB) is coordinated by the Paul-Ehrlich-Institut (DE). Local sera collections are kept and administered at the University of Amsterdam (NL), the University Hospital of Manchester (UK), Charité Berlin (DE) and Paul-Ehrlich-Institut, Langen (DE). The amounts of sera to be deposited depend on

the ethical approval and experimental necessities, but at least 15 and 3 ml of serum from adult and pediatric patients, respectively, will be kept. A barcode labelling system is used to facilitate sample identification and ensure patient identity. Case Record Forms are labelled with barcodes too. Serological data can be uploaded to the clinical databank via the internet interface. The EPASB coordinator and the partners managing the sera collections distribute serum samples for the experimental work. The serum bank coordinator and managing partners regulate access to the sera. The overall aim is to provide sera to fulfil EuroPrevall research goals. In co-operation with the partners requiring sera the EPASB coordinator and managing partners suggests appropriate sera panels for addressing specific diagnostic questions, for example evaluating component-resolved diagnostics in different peanut-allergic populations, or in fruit allergic subjects from different geographic regions in Europe.

In addition to sera from patients being allergic to the respective food, for which very detailed clinical data including threshold doses for eliciting subjective and objective allergic symptoms will be available, selection of control samples is very important. The strongest controls in a diagnostic study are those sera samples with a high likelihood of giving false positive results, for example resulting from clinically irrelevant cross-reactivity. Such controls may include:

IgE-positive subjects with negative DBPCFC.

Patients with atopic dermatitis but no food allergy.

Pollen-allergic subjects without food allergy such as:

- birch pollen-allergic subjects for studies in Central and Northern Europe,
- olive and/or plane pollen tree-allergic subjects for studies conducted in Spain, Italy and Greece,
- mugwort and ragweed pollen-allergic subjects for studies performed in France and some parts of Spain and Italy.

Mite-allergic subjects for studies on food allergy to crustaceans.

Other appropriate controls.

The serum bank will be maintained after termination of the project. Subsequent investigations, however, are only possible if these are in accordance with the original research goals of EuroPrevall since it is not possible to obtain ethical approval for unrestricted use of sample material from human individuals if the material is collected within a specific research project. Thus, sera remain property of the contributors and they have the final decision if an intended use suggested by one project partner was not specified in the project description. Even though this may seem restrictive the opportunity to participate in high impact research studies will entice the partners to further cooperate with each other. At the same time, this rule prevents using material from the serum bank for investigating additional interesting questions outside the scope of EuroPrevall, e.g. the potential allergenicity of genetically-modified foods.

## **5. Conclusions**

The EuroPrevall serum bank and the Clinical Databank are being developed as tools to facilitate the aims of the project. Standardised reporting of data collected across Europe is achieved and this data will directly be linked on an individual patient basis with serological and scientific data generated in other centers. By searching the databank, relevant clinical patterns can be identified and subsequently addressed in research studies. Thereby the clinical information always forms the basis of any use of sera panels taken from the EPASB.

## **Conflict of interest statement**

The authors declare that there are no conflicts of interest.


## **Acknowledgement**

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